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Original Article

# Patterns of Intravenous Human Immunoglobulin Administration in a Middle Eastern Teaching Hospital

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## Abstract

**Background:** Drug use evaluation (DUE) helps to investigate and modify the pattern of drug administration with the aim of improving patient care and cost saving. Considering the important indications for intravenous immunoglobulin (IVIG) and its high cost, assessment of its prescription pattern could be helpful in increasing the efficiency of the health system.This study aimed to investigate the pattern of IVIG use in a tertiary teaching hospital.

**Methods:** This retrospective study included all inpatients who received IVIG in spring and summer 2020. The needed information was extracted from patients' files. Data were analyzed using SPSS and compared with the standard guidelines.

**Results:** A total of 72 patients received IVIG. The indications were "FDA-approved" and "CEDIT-acknowledged" in 33.3% and 61.1% of the cases, respectively, and 45.8% adhered to the "red" indications of the UK protocol. Moreover, all prescriptions were in accordance with the approved indications of the FDO (Iranian Food and Drug Organization) guideline. Guillain-Barré syndrome (GBS), chronic inflammatory demyelinating polyneuropathy, and COVID-19 were the three most common causes of IVIG administration. Additionally, 66.7% had received the recommended dose regimen and 51.3% experienced drug side effects requiring some measures.

**Conclusion:** The occurrence of adverse drug reactions in more than half of the studied patients and related costs substantiate the need for enhancing physicians' refrain from the unnecessary prescription of the IVIG, nursing staff's knowledge, and the inclusion of a clinical pharmacist in the healthcare team.

**Keywords:** IVIG, Immune globulin, DUE, Drug use evaluation, Rational prescription

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## Introduction

Intravenous immunoglobulin (IVIG) is a costly biological product extracted from healthy donated plasma. The final product contains antibodies of all donors and includes 5-8 g/dL of protein, 90% of which is IgG (1). This product was introduced in 1980 to manage immunodeficiency, and by creating an appropriate concentration of antibodies, it has caused the removal of inflammation induced by a broad spectrum of pathogens in immunodeficient patients. In addition, it modulates the immune system in the treatment of autoimmune diseases. Today, its application has expanded to medical fields such as neurology, hematology, dermatology, nephrology, and rheumatology (2,3).

Irrational medicine prescription is a worldwide issue (4). Optimizing medication utilization not only reduces drug costs but also improves patients' outcomes regarding lower side effects and higher effectiveness (5). Drug use evaluation (DUE) is an effort to investigate the pattern of drug administration and, if necessary, modify it based on the standard guidelines (4). Studying the pattern of IVIG administration and utilization is considered an important research topic due to its important role in the control and treatment of many diseases, the increasing number of its indications and irrational prescriptions, the limited information on its proper use (especially in the Middle East), its high cost, and ultimately, scarce resources of preparation (2,6).

In recent years, the number of off-label indications for IVIG has expanded, but there is insufficient clinical evidence for many of them. The disease stage, severity, optimal circumstances, and the availability of less expensive substitutions with fewer side effects should also be considered (6,7). Despite the effectiveness and good tolerance in many cases, there are reports regarding the occurrence of serious side effects that must be considered (1). Many countries have addressed this issue and various policies have been devised to monitor and regulate the IVIG administration (8). In this regard, this study aimed

to evaluate IVIG utilization pattern in an educational hospital and compare it with international guidelines.

## Materials and Methods

This descriptive cross-sectional study was conducted with a retrospective design at Shahid-Beheshti Teaching Hospital in western Iran, affiliated with Hamadan University of Medical Sciences. In order to evaluate the pattern of IVIG prescription and utilization, all inpatients who received IVIG during a 6-month period (spring and summer 2020) were included in the study. The relevant data, such as demographic information (age, gender, and weight), laboratory and clinical parameters, admission ward, diagnosis, medication dosage, length of treatment, and side effects of medicines were obtained by reviewing patients' records. The compliance of the IVIG prescription with the guidelines developed by the FDA (United States Food and Drug Administration), the CEDIT (Committee for the Evaluation and Diffusion of Innovative Technologies), the FDO (Iranian Food and Drug Organization) and the UK protocol was also examined. SPSS was used for data analysis.

Based on the FDA guideline, the IVIG indications are subcategorized into three main categories: FDA-approved, Off-labeled with support (strong evidence showing its effectiveness), and Off-labeled without support (there is no evidence to substantiate its use) (6,7). In the CEDIT standard guideline, IVIG indications are classified into three subgroups: acknowledged, under assessment, and unwarranted (9). Considering the UK protocol, the indications are graded using four colors: (a) red: IVIG therapy is highly evidence-based and considered critical (the highest priority), (b) blue: the use of IVIG is based on reasonable evidence and should be modified when there is a shortage of this drug (moderate priority), (c) gray: IVIG treatment is based on weak evidence and should be planned for each case (the latest priority), and (d) black: the use of IVIG is not recommended (10). Finally, the FDO guideline lists the indications for the IVIG that is considered approved by this organization (11).

## Results

Table 1 summarizes the included cases' demographics and details of IVIG prescriptions. As shown in Table 1, out of 72 patients included in the study, 34 cases (47.2%) were male. The IVIG was prescribed for 15 different indications, described in detail in Table 1. The cases' age ranged from 19 years to 90 years, with a mean of 46.1 years, of whom 8 (11.1%) were elderly (65 years of age or older). Additionally, 17 patients (23.6%) were affected by diabetes mellitus, for whom some precautions had to be taken. Hydration was performed by infusion of 500 mL of 0.3% sodium chloride in 13.9% of IVIG recipients. Besides, 37 cases (51.38%), including 22 women and 15 men, experienced side effects after IVIG infusion. Moreover, 14 patients suffered from only one complication, while 23 cases had more than one complication. Shortness of breath (dyspnea) (11.1%), bleeding at the injection site (9.7%), nausea and vomiting (8.3%), and infection (8.3%) were the four most frequent side effects. Among the patients experiencing side effects, 3 cases (4.1%) had a high initial infusion rate, which was adjusted by the physician.

Based on the records, clinical and laboratory parameters of each patient had been assessed before IVIG infusions, and renal function was continuously monitored. Unfortunately, 10 patients expired during the therapy, 4 of whom were infected with COVID-19. The remaining 62 patients were discharged after treatment completion.

The most common reason for prescribing IVIG was Guillain-Barré syndrome (GBS) (25%), which adhered to the "off-labeled with support" category of the FDA guideline, the "acknowledged" subgroup of the CEDIT guideline, "red" indications of the UK protocol, and approved groups of the FDO protocol.

A total of 1377 vials of IVIG (6885 g) were administered during this study period, of which 388 vials (2020 g) and 908 vials (4540 g) were consumed for the indications approved by the FDA and the CEDIT guidelines, and 747 vials (3735 g) were utilized for the "red" indications of the UK protocol. Moreover, except for the amount used to treat COVID-19 (605 g), the amount of IVIG administration (6280 g) for all indications was approved by the FDO guideline (Table 1).

Considering IVIG administration based on the ward, the majority (4,615 g, 67%) of IVIG prescriptions belonged to the neurology ward. The number of patients and the amount of administered IVIG in each ward have been summarized in Table 1. Regarding the treatment length, the minimum and maximum lengths were 1 and 5 days, with a median of 4 days.

In terms of dosage, the standards state that the dose of IVIG should be calculated based on the patient's body weight. In the present study, the weight of the patients varied from 35 kg to 100 kg, with a mean of 66.47 kg. In 48 patients (66.7%), the prescribed dose was in accordance with guidelines, 5 cases (6.9%) received a dose higher than the recommended one, and 7 cases (9.7%) experienced an underprescribing. It might be worth mentioning that in the case of 12 patients, guidelines have not determined any recommended dose for IVIG, because the effectiveness of this medicine in these cases has not been proven. Additionally, 10 patients (13.9%) were infected with coronavirus, 1 case had adult-onset Still's disease (AOSD), and 1 case was a pregnant woman with vaginal bleeding and a history of spontaneous miscarriage.

The 15 observed indications for IVIG administration in this study were categorized based on the FDA guideline, the CEDIT guideline, and the UK protocol (Figures 1, 2, 3 and Table 1). Regarding the FDO guideline, the IVIG prescription was approved for all cases.

Considering the FDA guideline, the highest percentage of IVIG use was assigned to the "off-labeled with support" indications (44.4% of patients). The percentage of IVIG administration for the "FDA-approved" and "off-labeled

**Table 1.** Patients' Demographics and Details of IVIG Prescriptions

| Variable | Results |
|---|---|
| **Patients' demographics** | |
| Age (year) | 19 – 90 |
| Gender (n) (%) | 34 (47.2) male and 38 (52.8) female |
| Weight (kg) | 35 - 100 |
| **Details of IVIG prescriptions** | |
| **Hospital ward in which IVIG prescribed** | **(n)(g)** |
| Neurology | (41) (4615) |
| Oncology / Hematology | (10) (785) |
| Nephrology | (7) (570) |
| Infectious disease | (6) (410) |
| Respiratory | (5) (155) |
| Rheumatology | (3) (350) |
| **Cause of IVIG administration** | **(n) (%) (g)** |
| Guillain-Barre syndrome (GBS) | (18) (25) (2340) |
| Chronic inflammatory demyelinating polyneuropathy | (CIDP) (11) (15.3) (1055) |
| COVID-19 | (10) (13.9) (605) |
| Bronchiectasis due to secondary acquired hypogammaglobulinemia | (4) (5.6) (80) |
| Idiopathic thrombocytopenic purpura (ITP) | (4) (5.6) (340) |
| Kidney transplantation rejection | (4) (5.6) (420) |
| Multifocal motor neuropathy (MMN) | (MMN) (4) (5.6) (425) |
| Systemic lupus erythematosus (SLE) | (4) (5.6) (295) |
| Autoimmune encephalitis | (3) (4.2) (350) |
| Polymyositis | (3) (4.2) (265) |
| Myasthenia gravis | (2) (2.8) (180) |
| Multiple sclerosis (MS) | (2) (2.8) (225) |
| Disseminated intravascular coagulation (DIC) associated with systemic vasculitis | (1) (1.4) (60) |
| Chronic lymphocytic leukemia (CLL) | (1) (1.4) (120) |
| Adult-onset Still's disease (AOSD) | (1) (1.4) (125) |
| Consumed IVIG (g) | 6,885 |
| **Adherence to FDA guideline** | **(n) (%) / (g)** |
| FDA approved | (24) (33.3) / (2020) |
| Off-Labeled with support | (32) (44.4) / (3780) |
| Off-Labeled without support | (6) (8.4) / (480) |
| COVID-19 | (10) (13.9) / (605) |
| **Adherence to UK guideline** | **(n) (%) / (g)** |
| Red | (33) (45.8) / (3735) |
| Blue | (18) (25) / (1490) |
| Gray | (8) (11.1) / (705) |
| Black | (3) (4.2) / (350) |
| COVID-19 | (10) (13.9) / (605) |
| **Adherence to CEDIT guideline** | **(n) (%) / (g)** |
| Acknowledged | (44) (61.1) / (4540) |
| Under assessment | (12) (16.7) / (1220) |
| Unwarranted | (6) (8.3) / (520) |
| COVID-19 | (10) (13.9) / (605) |
| **Adherence to FDO guideline** | **(n) (%) / (g)** |
| Yes | (62) (86.1) / (6280) |
| No | (-) (0) |
| COVID-19 | (10) (13.9) / (605) |
| **Adverse drug reactions** | **(n) (%)** |
| Shortness of breath (dyspnea) | (8) (11.1) |
| Bleeding at the injection site | (7) (9.7) |
| Infection/nausea and vomiting | (6) (8.3) |
| Allergic reactions/constipation/ fever and chills/hypotension/skin rashes | (5) (6.9) |
| Itching/weakness | (4) (5.6) |
| Headache/loss of consciousness/ shock/urinary retention | (3) (4.2) |
| Thrombosis | (2) (2.8) |
| Bradycardia/chest pain/cough/ increased heart rate/increased serum creatinine/meningitis/night sweats/seizures/stomach pain/ swallowing disorders (dysphagia) | (1) (1.4) |

IVIG: intravenous immunoglobulin, FDA: food and drug administration, UK: United Kingdom, CEDIT: committee for the evaluation and diffusion of innovative technologies, FDO: Iranian food and drug administration

without support" indications was 33.3% and 8.4%, respectively. Based on the CEDIT guideline, 61.1% of the indications were assigned to the "acknowledged" subgroup, and the percentage of IVIG administration for "under assessment" and "unwarranted" indications of this guideline was 16.7% and 8.3%, respectively. Considering the UK protocol, the prescription of IVIG adhered to the "red," "blue," "gray," and "black" indications in 45.8%, 25%, 11.1%, and 4.2% of the cases, respectively. Additionally, 10 of the 72 cases (13.9%) were infected with coronavirus and received IVIG as supportive care. However, during our study period, there was not any recommended dose regimen in the guidelines, and this indication was not included in any of the mentioned categories.

## Discussion

IVIG is a costly blood product employed for the treatment of various pathological conditions by raising antibody concentrations (1,2). Several probable mechanisms for the effects of this product have been identified, but the

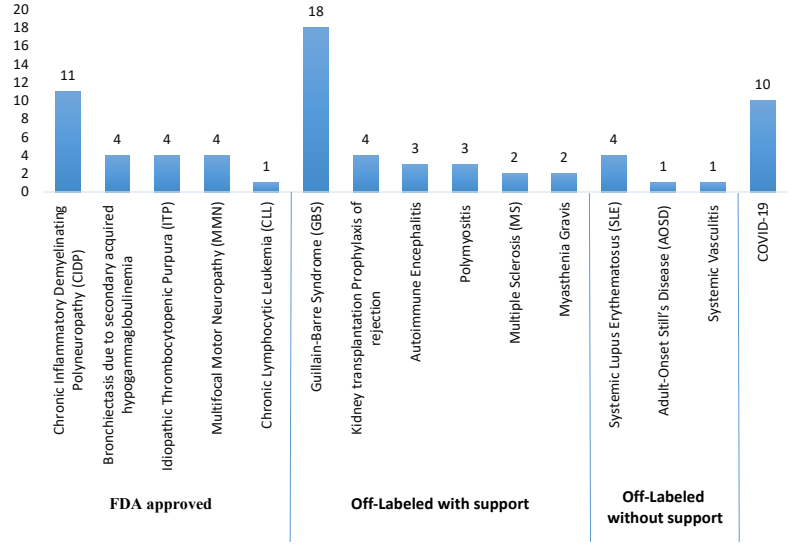


**Figure 1.** Indications for IVIG Administration Based on the FDA Guideline

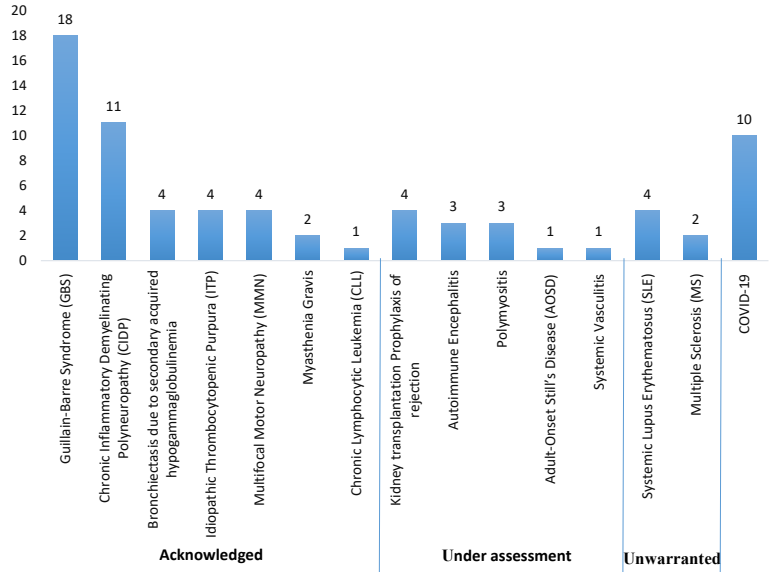


**Figure 2.** Indications for IVIG Administration Based on the CEDIT Guideline

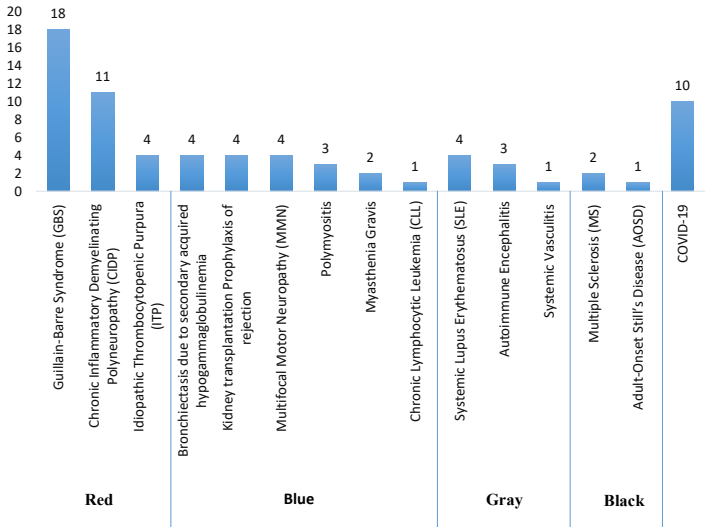


**Figure 3**. Indications for IVIG Administration Based on the UK Guideline

relative contribution of each mechanism to the various disorders remains uncertain (1). Considering the limited access to IVIG around the world, increasing unlicensed usage, high production costs, possible adverse reactions, and inadequate information on its effectiveness, especially in the Middle East, physicians need to take special precautions while using this drug properly. Evaluation of IVIG misuse has been one of the priorities of healthcare providers for the past several years (6,12,13). DUE studies can help to investigate the pattern of drug consumption and, if required, modify it based on standard guidelines (5). The findings of DUE can help physicians to improve the quality of their prescriptions, which in turn enables policy-makers in the health care systems to make better decisions and plans.

The FDA has approved the use of IVIG for the following purposes: treatment of primary immunodeficiency, prevention of bacterial infections in secondary immunodeficient individuals with hypogammaglobulinemia and chronic lymphocytic leukemia (CLL), prevention of coronary artery aneurysms in Kawasaki disease, increase of platelets counts in idiopathic thrombocytopenic purpura (ITP) to prevent or control bleeding, reduction of serious bacterial infection in HIV-infected children, prevention of infections and pneumonitis in acute graft-versus-host disease, chronic inflammatory demyelinating polyneuropathy (CIDP), and multifocal motor neuropathy (MMN) (6). Many organizations and nations have IVIG administration protocols. The current research examined the pattern of IVIG consumption in a teaching hospital and assessed its adherence to four guidelines belonged to the FDA, CEDIT, UK, and FDO guidelines.

In our study, 18 hospitalized patients (or 25%) received IVIG for GBS. The remaining indications were as follows: CIDP (15.3%), COVID-19 (13.9%), bronchiectasis due to secondary acquired hypogammaglobulinemia, ITP, kidney transplantation rejection, systemic lupus erythematosus (SLE), and MMN (with the same percentage of 5.6%), polymyositis and autoimmune encephalitis (AE) (each 4.2%), multiple sclerosis (MS) and myasthenia gravis (MG) (each 2.8%), and ultimately, CLL, AOSD, and systemic vasculitis (with the same percentage of 1.4%). The frequency of FDA-approved indications such as CIDP, ITP, MMN, CLL, and bronchiectasis due to secondary acquired hypogammaglobulinemia was 33.3% in our study, which is comparable to a similar study conducted on IVIG consumption at King Khalid University Hospital over a 3-year period. In that study, 305 patients were identified, and 109 of them (35.7%) received IVIG for FDA-approved indications (13).

Speaking about adherence to the guidelines, 61.1% of IVIG indications were assigned to the "acknowledged" subgroup of the CEDIT guideline, which agrees with what Frauger et al discovered in another study conducted in three French university hospitals in 2006. In other words, 70% of IVIG indications were assigned to the "acknowledged" subgroup of the CEDIT guideline, and 9% and 18% of IVIG prescriptions were for "under assessment" and "unwarranted" indications, respectively (9). It has been reported in previous studies that despite the availability of comprehensive guidelines, physicians sometimes prescribe this product in situations where it has not been recommended or as a last resort when conventional treatments have failed. Overall, more than half of IVIG prescriptions worldwide were for indications that are not approved by the FDA. Among them are hemolytic disorders of neonates who do not respond to phototherapy, prevention of the incidence of nosocomial infections in neonates born weighing less than 2500 grams, AIDS-related thrombocytopenia, multiple myeloma associated with hypogammaglobulinemia, autoimmune hemolytic anemia, GBS, MS, MG, solid organ transplantation, dermatomyositis, necrotizing fasciitis, and so on. Patterns of IVIG utilization continue to change (14). It is worth noting that during our six-month observation period in 2020, the spread of the coronavirus was a significant issue; in fact, 13.9% of all hospitalized patients were infected with this virus and received IVIG. The multifunctional long-term effects of immunoglobulin therapy make it a suitable therapeutic candidate for patients hospitalized with COVID-19. After GBS and CIDP, COVID-19 was the third most frequent indication for IVIG. However, there was no recommendation on the dose, timing, or rate of IVIG infusion in our employed guidelines during the study period.

Considering the adverse drug reactions, in a study by Björkander et al, conducted on 49 patients receiving IVIG, only 4.7% of them experienced adverse drug reactions related to IVIG infusion (15). Ruiz-Antorán et al studied systemic reactions to IVIG in 13 Spanish hospitals. A total of 119 patients (21.4%) experienced infusion-related adverse effects. In 28 (5%) of them, this complication was serious, and in 96 patients (17%), the infusion was stopped or modified (16). In contrast, more than half of the IVIG patients in our study (37 of them, or 51.38%) experienced adverse drug reactions, which is significantly more than what was reported in earlier studies. More than half of the patients (51.4%) who indicated adverse drug reactions had IVIG infusions for "off-label with support" indications, 32.4% had IVIG infusions for the "FDA-approved" indications, and 2.7% had infusions for "off-label without support" indications. Additionally, 10.8% of the patients who experienced infusion-related adverse effects were infected with COVID-19. In the case of the CEDIT guideline, 67.6%, 18.9%, and 2.7% of patients with complications belonged to the "acknowledged", "under assessment", and "unwarranted" indications, respectively. Based on the UK protocol, 51.4%, 27%, 5.4%, and 5.4% of patients with reported complications followed the "red", "blue", "gray", and "black" indications, respectively.

Based on the literature, the majority of adverse drug reactions are mild and are consequences of a high infusion rate, infection, brand change, the patient's sensitivity,

and the initial infusion (17,18). In Iran, IVIG is not accessible in a generic form, and a commercial product may not always be available. Obviously, it is vital to follow the manufacturer's suggested infusion instructions. By performing premedication, taking the right precautions, and infusing IVIG at a rational rate, the possibility of adverse drug effects will be greatly reduced (19). Patients with a history of renal failure, patients who take nephrotoxic medicines, patients over 65 years old, patients with diabetes, and cardiovascular patients should be hydrated prior to receiving an infusion (20). In the study conducted by Brennan, 41% of adverse drug reactions happened in patients who needed to take pre-infusion measures. Staff and patients who administer IVIG infusions need to be evaluated and educated regularly to lower the risk of side effects (19).

When it comes to the rational medication, the appropriate dosing should also be addressed. The dose of IVIG should be calculated based on the patient's body weight. In our study, more than half of the cases (66.7%) received the recommended dose, 5 cases (6.9%) received more, and 7 cases (9.7%) received less. In October 2010, pharmacist-led research at Brigham and Women's Hospital focused on IVIG dosing per ideal body weight for each indication. There were a total of 418 patients. For 2.2% and 0.5% of them, doses and administration frequencies were not in compliance with the related guideline (21). A cross-sectional study performed in a teaching hospital located in the east of Iran reported that about half of the cases had received the recommended dose regimen, around one-third (28.6%) received a dose less than the recommended one, and 2 cases (4.1%) received an excess dose (22).

GBS was the most common IVIG prescription in this research. Plasmapheresis may be used in addition to IVIG to relieve the patient's symptoms. Plasma exchange and IVIG infusion are equally effective treatments for GBS. However, IVIG is substantially more expensive (23). Plasmapheresis and corticosteroid therapy are two other therapy choices for the treatment of CIDP, which was the second most common indication for IVIG prescription. Each of the three treatment approaches has both advantages and disadvantages, and their efficacy is comparable (24).

Our research had some limitations, including a small sample size and insufficient patient medical records, such as infusion length, in the patients' files.

## Conclusion

It was revealed that, in the studied patients, IVIG was widely utilized for "off-labeled" and "unwarranted" indications. The lack of evidence on the effectiveness of IVIG in many situations, the high cost of production, and the limited procurement resources all substantiate the necessity for regular follow-ups. Practitioners should administer this medicine with more caution and avoid prescribing it inappropriately. Overprescription of a medicine might cause negative health effects, higher treatment expenses, and treatment failure. One of the main aims of drug utilization evaluation is to cut down on direct and indirect drug costs caused by irrational prescriptions. Most Iranian hospitals suffer from a lack of human resources. Participation of the pharmacy department in medicine preparation and the inclusion of a clinical pharmacist in the healthcare team can improve treatment outcomes, prevent avoidable adverse drug reactions, and reduce treatment costs for patients and society. In this research, for the first time, two European guidelines and the FDO guideline were applied along with the FDA guideline. Based on the findings, it is recommended that interventional trials on IVIG be conducted to provide the evidence needed to develop regional and national recommendations, as well as studies to find strategies for better control of the related costs.

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### Authors' Contribution

**Conceptualization:** Maryam Etminani.
**Data curation:** Yasmin Zabihi, Maryam Rangchian.
**Formal analysis:** Maryam Rangchian.
**Methodology:** Maryam Etminani.
**Project administration:** Maryam Etminani, Maryam Rangchian.
**Writing – original draft:** Yasmin zabihi.
**Writing – review & editing:** Maryam Rangchian, Maryam Etminani.

### Competing Interests

The authors declare that they have no conflict of interests.

### Ethical Approval

Ethics Committee of Hamadan University of Medical Sciences examined and approved the study protocol (ID: IR.UMSHA.REC.1399.602).

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